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Research Article

Role of procalcitonin in the diagnosis of neonatal sepsis.

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Abstract

Objective: Early diagnosis of neonatal sepsis and appropriate treatment decreases the mortality and morbidity of these infants. The aim of this study was to assess the role of procalcitonin (PCT) as a marker in the early diagnosis of neonatal sepsis. **Materials and Methods:** 35 neonates with early onset sepsis (admitted to the Neonatal Intensive Care Units at El-Minia Children University Hospital (from August 2012 to August 2013) were included in the study. Another 35 healthy neonates with no clinical and biological data of infection were taken as control, they were subjected to thorough history taking, routine laboratory investigations and serum PCT and C-reactive protein (CRP) were determined by ELISA. **Results:** Mean levels of PCT and CRP in neonates with sepsis were significantly higher than the control. There was a significant moderate positive correlation between PCT and C-reactive protein and insignificant correlation between procalcitonin and total leukocytic count among the neonates with sepsis. Also procalcitonin had high sensitivity, specificity, high positive predictive value and high negative predictive value. procalcitonin showed higher sensitivity in comparison to that of CRP. **Conclusion:** Procalcitonin is a sensitive, independent and useful biomarker than CRP in early diagnosis of neonatal sepsis.

Keywords: Procalcitonin, C-reactive protein, Neonatal sepsis.

Introduction

Neonatal sepsis is a common cause of morbidity and mortality in newborn infants. Two patterns of disease, early- onset (<7 days of birth) and late-onset (>7 days) have been associated with neonatal sepsis (1). Rapid diagnosis and treatment of systemic bacterial infection are essential in neonate and infants, since a delay in treatment of severe bacterial infection may not lead to a proper Outcome (2). The clinical findings of sepsis are uncertain in newborn infants and these findings may be associated with multiple conditions beside infection. Therefore antibiotics are started immediately in newborn who have nonspecific findings of infection and are continued until the final result of the blood culture is obtained (3).

Blood culture can remain negative despite bacterial sepsis. The difficulty in making early diagnosis of neonatal sepsis is noted despite improved bacteriologic techniques, therefore a group of tests were studied to assess their usefulness either singly or in combination in predicting neonatal sepsis. Determination of procalcitonin (PCT) is another laboratory study which supports the diagnosis (4).

In 1993 PCT was first described as a marker of the extent and course of systemic inflammatory response to bacterial and fungal infections (5). Procalcitonin (PCT) propeptide is the precursor protein of calcitonin and has no hormonal

activity. It is a glycoprotein having 116 amino acid proteins with a molecular mass of 14.5k Da (6). Normally it is produced by the C cells of the thyroid gland. In healthy persons procalcitonin levels are undetectably low. But in severe bacterial, fungal, parasitic infections with systemic manifestations, a significant rise in procalcitonin levels are seen. In this condition the production site is

the extra thyroid tissues (7,8). It was shown in healthy volunteers that PCT is detectable in the plasma two hours after the injection of a small amount of bacterial endotoxins, increasing rapidly in 6-8 hours, and reaching a plateau between 12 and 48 hours (9). PCT levels increase in severe sepsis and its plasma concentration is related to the patient's clinical condition. Serum PCT levels appeared to correlate with the severity of microbial invasion (10).

CRP is one of the acute phase proteins. Although it is a classical and sensitive marker of inflammation; it cannot be used to differentiate between bacterial and other infection. It is a disadvantage that CRP increases after PCT. This is why; several authors have opined that it is important to be cautious with the interpretation of CRP values in children with fever lasting less than 12 hours because at that time it may remain negative although there is presence of sepsis. (6). Noninfectious condition, as perinatal asphyxia, respiratory distress syndrome, brain hemorrhage and meconium aspiration syndrome and post surgical period can induce abnormal values of CRP(11,12). In contrast localized bacterial infections, severe viral infections and inflammatory reactions of noninfectious origin do not or only slightly increase PCT level (13). The increase of PCT has been observed before the rise in CRP(6) The unique feature that PCT levels increase in bacterial and fungal infections, but remain unchanged even in severe viral infections and other inflammatory diseases, makes PCT attractive as a potential diagnostic variable for the diagnosis of bacterial infection.(14)

Aim of the study

The present study aimed at investigating the validity value of PCT versus CRP, in establishing the early diagnosis of neonatal sepsis.

Materials and Methods

Study population

A descriptive cross-sectional study, 35 neonates with early onset sepsis admitted to the Neonatal Intensive Care Units (NICU) at El-Minia Children University Hospital (from August 2012 to August 2013) were included. Written consent was obtained from the families of all the investigated neonates.

Inclusion criteria: Any suspected case of neonatal sepsis with maternal risk factors for sepsis e.g. prolonged labor, premature rupture of membrane (PROM) or prolonged PROM >18 hours, maternal intrapartum fever, urinary tract infection (UTI), chorioamnionitis and clinical signs and symptoms of the newborn having sepsis : temperature instability, apnea, need for supplemental oxygen, need for ventilation, bradycardia, tachycardia, hypotension/ hypoperfusion, feeding intolerance, abdominal distension, necrotizing enterocolitis.

Exclusion criteria were; administration of antibiotic therapy prior to admission, birth asphyxia, aspiration syndromes, laboratory finding suggestive of inborn error of metabolism and congenital anomalies. Another 35 neonates apparently healthy cross matched with age and sex were taken as control group.

Before initiation of antibiotic therapy in infants suspected of sepsis, blood samples for complete blood count, blood culture (1-2 ml), PCT and CRP measurements (1-2 ml) were obtained by peripheral venous puncture. Serum was separated from blood cells by centrifugation and stored in 2 plastic tubes at -20 °C for measurements of PCT and CRP.

PCT measurement

Procalcitonin assay was measured by using a commercial enzyme-linked immunosorbent assay kit. Level more than 1.1pg/ml is considered positive (Procalcitonin in Human EIA Kit, EK-031-30; Phoenix Pharmaceuticals, Inc., Belmont, CA, USA).

CRP measurement

Serum C-reactive protein was determined by standard nephlometric method. Level more than 12 mg/dl is considered positive

Statistical analysis

Data was analyzed by using SPSS (version 16 software). The following statistical tests were used:

1. Mean and standard deviation (SD) to describe quantitative data.
2. Student t test was used to compare between two groups as regards parametric data.
3. Chi-square test was used to compare between two groups as regards non-parametric data.
4. Pearson correlation was used to correlate two quantitative variables.
5. Recover operating character (ROC) analysis to evaluate sensitivity, specificity, and positive and negative predictive values of procalcitonin and CRP levels as diagnostic tests. For all tests, a probability (p) of less than 0.05 was considered significant.

Results

In this study, 35 neonates with positive blood cultures and clinical sepsis (group I) were enrolled as cases and 35 healthy neonates were enrolled as control (group II) was enrolled. Table1 showed higher incidence of sepsis among males compared to female, It also showed that neonates born by CS had a significant higher reading than neonates born vaginally (P=0.04).Neonates with sepsis had a significant higher total leukocytic count, bilirubin(total and direct) level than the control group (P=0.001). Also, showed that C- reactive protein and procalcitonin levels had a significant higher readings among cases than controls (p=0.0001) (table 2) As regard the sensitivity and specificity values, PCT had higher sensitivity , higher NPV than CRP, while CRP had higher specificity , higher PPV in comparison to PCT. (table 3).

Table 4 showed that C-reactive protein had a significant moderate positive correlation with Procalcitonin (r=-0.55, p=0.001). Also there was insignificant correlation between PCT and TLC among group I (r= -0.20, p=0.2).

Table 1: Demographic and clinical characteristics of the studied cases and controls.

characteristics		Group I (Cases) No=35	Group II (Controls) No=35	Chi-square	P value
Gestational age	Full term Pre term	21 (60%) 14 (40%)	25 (71.4%) 10 (28.6%)	1.01	**0.4**
Sex	Male Female	19 (54.3%) 16 (45.7%)	13 (37.1%) 22 (62.9%)	2.07	**0.1**
Gestational weight	Range Mean ±SD	750-3700 2575.1±842.5	1400-3500 2665.7±685.3	0.49	**0.6**
Mode of delivery	Normal C S	15 (42.6%) 20 (57.4%)	26 (74.3%) 9 (25.7%)	7.12	**0.04***
Apgar	score 1 score 5	6.29±2.3 7.8±1.57	8.1±1.3 9.13±0.8	0.5	**0.18** **0.15**
Blood culture	**Positive** **Negative**	**35(100%)** **0**	**0** **35(100%)**	**70.000**	**0.0001***

C S caesarian section

Table 2: Comparison between neonates with sepsis and control group as regard the laboratory findings;

Characters		Cases No=35	Controls No=35	T test	P
Total leukocytic count (/µl)	Range Mean ±SD	9.5-20.1 16.06±2.9	8-11 9.2±0.5	13.8	**0.001***
Hb (gm%)	Range Mean ±SD	11.3-18.4 16.4±1.7	11-14 12.5±1.4	0.48	**0.5**
Total bilirubin (mg/dl)	Range Mean ±SD	7.6-20 12.5±4.1	2-8 5.6±2.3	8.68	**0.001***
Direct bilirubin (mg/dl)	Range Mean ±SD	1-2.3 1.03±0.6	0.5-1 0.7±0.3	2.71	**0.001***
CRP	Range Mean ±SD	52.5-151.1 85.6±44.4	5.6-11.6 8.09±11.1	10.22	**0.0001***
Procalcitonin level (pg/ml)	**Range Mean ±SD**	**52.5-556.3 185.6±144.4**	**5.6-110.6 48.09±31.1**	**5.51**	**0.0001***

*significant, Hb: Hemoglobin level CRP: C-reactive protein

Table 3: The sensitivity, the specificity , PPV and NPV of PCT and CRP.

	cut-off value	**Sensitivity**	**specificity**	**PPV**	**NPV**
CRP	12 mg/l	72.9 %	100 %	93.2 %	69.7 %
Procalcitonin	1.1 pg/ml	80 %	85.7 %	84.8 %	81.1 %

CRP= C-reactive protein, PPV= Positive predictive value, NPV= Negative Predictive value

Table 4: correlations between Procalcitonin and both CRP and total leukocytic count(TLC) among group I

Group 1(cases)		CRP	TLC
procalcitonin	p	0.001*	**0.2**
	R	**0.55**	**0.2**

TLC: total leukocytic count

Discussion

Twenty obese patients were enrolled in this study. Among the patients included there were 11 men (55%) and 9 women (45%). The age of the patients had a mean of 35.1 ± 11.116 years. Mean initial weight was 113.45 ± 11.83 Kg. Mean height was 1.745 ± 0.049 meters. Mean baseline BMI was 37.47 ± 4.045 Kg/ m^2.

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteraemia in the first month of life Constellation of signs and symptoms is caused by micro-organisms or their toxic products in blood (15). The diagnosis of neonatal sepsis is difficult, because clinical signs of sepsis often overlap with other non-infectious causes of systemic inflammation (16) . There is no single reliable test for the early definite diagnosis of neonatal sepsis and therefore , there is a continuing search for a new marker aiming to differentiate between sepsis and non- infectious conditions , among them Procalcitonin (17).

In this study sepsis was more common in male (62%) than female (38%), which is consistent with the findings of Washburn et al.(18). This is probably due to the attitude of the parents who seek medical services more for their male babies than female babies in this region. It was seen that infection was more common in the low birth weight baby compared to babies of normal birth weight in studies reported from India, Bangladesh (19) as is also in our study. Out of 35 cases of sepsis, caesarean section was found in 57.4% and normal delivery in 42.6% cases. This is probably due to increased number of high risk pregnancies admitted in this hospital leading to increased caesarean section. This is similar to studies by Tuuli and Odibo (20) and Afsharpaiman et al (21)who reported that neonates delivered via cesarean section had higher chances of developing neonatal sepsis in comparison to neonates delivered via vaginal delivery. They demonstrated that cesarean section can be associated with several adverse neonatal events such as respiratory complications. This leads to higher NICU admissions and higher chances of developing newborn sepsis.

Regarding laboratory data of neonates included in the study , there were significant higher levels of total leukocytic count in neonates with sepsis than the control group (p=0.001). This finding was comparable with that of the studies by Basu S et al ., (22) and Srinivasan and Harris (23) They concluded that total leukocytic count (TLC) is useful to estimate the probability of sepsis. However, Laurent R et al ., (24) found that total leukocytic count had a little value in discriminating neonates with infection. In this study CRP was significantly higher in neonates with sepsis (p=0.0001) (table 2). These results were in agreement with Chiesa C et al ., (25), Naglaa F et al ., (26) and Nora Hofer et al ., (27).They found that CRP was the most used laboratory test , it is accurate for the diagnosis of neonatal sepsis and being easily measurable and more affordable , it can be conveniently used as a good marker for the diagnosis of neonatal sepsis especially with poor resources . However Whicher J et al (6) and Naher BS et al (14) had reported that CRP is not necessarily diagnostic for sepsis as elevations may as well occur due to the physiologic rise after birth or non-infection associated conditions. As regards PCT concentration , the current study detected a significant higher levels of PCT in newborns with sepsis compared to the control group (p=0.001) . This was in agreement with many studies by Koksal N et al ., (28), Zahedpasha Y et al ., (29), and Sucilathangam G et al ., (30) . So , PCT may be helpful as an independent biomarker and it seems to be a better differentiating biomarker as it helps differentiating bacterial infection from viral infection . Also it correlates well with the progression and the severity of the infection. For this reason , PCT may be used not only as a marker of infection , but more importantly as a good marker of the severity of infection. They reported that PCT had beneficial diagnostic value and its measurement is helpful in early diagnosis

of neonatal sepsis. Also Dimple An and et al (31) found that PCT level increases rapidly in bacterial infection and restores to normal more rapidly than CRP and hence can be used to guide antibiotic therapy. This study demonstrated that, there were insignificant difference between the two studied groups as regard the correlations between PCT and gestational age , weight and neonatal jaundice respectively. However, there was a significant moderate positive correlation between PCT and CRP, (r=-0.55 ,p=0.001). This finding was consistent with that reported by some studies such as Vincent JL , Mercan D ., (32) , Lobo SM et al ., (33), and Mamdouh M et al ., (34) They found significant correlation between PCT and CRP. In contrary , a study by Wang et al .,(35) showed insignificant correlation between PCT and CRP. This study found insignificant correlation between PCT and TLC among the neonates with sepsis (r=-0.20 , p > 0.05). This finding was in agreement with that of waad Mahmood R et al .,(36) and Wang et al .,(35) . This was in contrary with the result of Srinivasan and Harris (23) they found significant correlation between PCT and TLC. This study showed that the sensitivity of PCT for the diagnosis of neonatal sepsis was (80%),the specificity was (85.7%) ,its PPV was (84.8%) and NPV was (81.1%).The sensitivity of CRP was (72.9%) , the specificity was (100%), its PPV was (93.2%) and its NPV was (69.7%), These results stated that PCT was more sensitive than CRP. The higher sensitivity of PCT in comparison to CRP was reported by some studies Pavcnik-Arnol et al ., (37) and Ivancevic et al ., (38), which proves that PCT could be used as a prognostic marker for the diagnosis of sepsis. In contrary , a study by Jimenez et al .,(39) reported higher sensitivity of CRP than PCT. Inconsistent with our results , the specificity of PCT was found to be lower than that of CRP in different studies by Janota et al ., (40) and Mamdouh M et al ., (34). They concluded that the lower specificity of PCT can be related to the multi organ dysfunction of the neonates who did not have sepsis . On the other hand, a study by Vazzalwar et al .,(41) showed that PCT has higher specificity than CRP. In this study, PPV of CRP was higher than that of PCT while NPV of PCT was higher than that of CRP. This was in the agreement with Abdollahi et al (42). However , a study by Sakha K et al ., (43) reported that CRP had higher NPV than PCT In neonates , an elevated PCT level may help in predicting septicemia ; furthermore , low PCT levels were helpful in ruling out septicemia as a diagnosis .The good negative value found suggested that PCT is a rapid and highly discriminative ; means to rule out bacteraemia . Therefore, PCT assessment could help the physicians in limiting the number of prescriptions for antibiotics.

Conclusions and Recommendations

PCT is a sensitive, independent and useful biomarker of neonatal sepsis. It correlates with the severity of sepsis. Additional measurement of CRP may increase the specificity. In patients with elevated serum CRP level, PCT may be used as a measure to support further the diagnosis of neonatal sepsis. We conclude that clinical evaluation seems to be the most reliable method in diagnosis, although all markers including PCT help us as supportive evidence. As this a study included a small group of population, we recommend further studies in a large number of populations to confirm the role of PCT in the diagnosis of neonatal sepsis.

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